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EXAMINER	
BOESEN, CHRISTIAN C	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/589,347	INAZAWA ET AL.	
	Examiner	Art Unit	
	CHRISTIAN BOESEN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-12* is/are pending in the application.

4a) Of the above claim(s) *9-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Final Office Action is responsive to the communication received 04/13/2010.

Claim Status

Claim(s) 2 have been canceled as filed on 04/13/2010.

Claim(s) 1, 3-4 and 7-8 have been amended as filed on 04/13/2010.

Claim(s) 1 and 3-12 are currently pending.

Claim(s) 9-12 have been withdrawn.

Claim(s) 1 and 3-8 are being examined in this application.

Election/Restrictions

Applicant's election without traverse in the reply filed on 08/13/2009 of group I, claims 1 and 3-8 is noted. Applicant has elected the following species: A. the CGH method (claims 3-4); B. ABCB1 gene (claim 6). New/amended claim(s) 1, 3-4 and 7-8 are grouped with the elected group I invention.

Priority

This application is filed under 35 U.S.C 371 of PCT/JP04/01574 (filed on 02/13/2004).

Claim Objection(s) Withdrawn

Upon further consideration and in light of Applicant's arguments and/or amendments, the following claim objection(s) as set forth in the previous office action is(are) withdrawn:

1. Claim 1 is objected to because of the following informalities: The claim recites the acronym "ABC" in line 3 of claim 1, is withdrawn due to the Applicant's amendments.

2. Claim 3 is objected to because of the following informalities: The claim recites the acronym "CGH" in line 2 of claim 3, is withdrawn due to the Applicant's amendments.

3. Claim 3 is objected to because of the following informalities: The claim recites "nethod" in line 1 of claim 3, is withdrawn due to the Applicant's amendments.

4. Claim 7 is objected to because of the following informalities: The claim recites "... as in index." in line 7 of claim 7, is withdrawn due to the Applicant's amendments.

5. Claim 8 is objected to because of the following informalities: The claim recites "substrte" in line 2 of claim 8, is withdrawn due to the Applicant's amendments.

6. Claim 8 is objected to because of the following informalities: The claim is missing "the" where the claim recites "wherein" the "DNA fixed on said" on line 2 of claim 8, is withdrawn due to the Applicant's amendments.

Claim Rejection(s) Withdrawn

Upon further consideration and in light of Applicant's arguments and/or amendments, the following claim rejection(s) as set forth in the previous office action is(are) withdrawn:

1. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn due to the Applicant's amendments.

A. Claim 3 recites the limitation "the CGH method, the flow cytometry method, the ELISA method, the DNA chip method, or the quantitative PCR method" in line 2 of claim 3, is withdrawn due to the Applicant's amendments.

B. Claim 4 recites the limitation "the CGH method or the DNA chip method" in line 2 of claim 4, is withdrawn due to the Applicant's amendments.

C. Claim 7 recites the limitation "the DNA of a test cancer cell" in line 2 of claim 7, is withdrawn due to the Applicant's amendments.

D. Claim 7 recites the limitation "said DNA-fixed substrate" in line 4 of claim 7, is withdrawn due to the Applicant's amendments.

E. Claim 7 recites the limitation "the test DNA" in line 6 of claim 7.

2. Claim 1 is indefinite and unclear in their recitation for being incomplete by omitting essential steps or ingredients, such omission amounting to a gap between the steps, is withdrawn due to the Applicant's amendments.

3. Claim 7 is indefinite and unclear in the recitation of “the fluorescent dye obtained as a result of the hybridization as in index.”, is withdrawn due to the Applicant's amendments.

New Claim Objection(s)

Claim Objections

Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Amended Claim 1 has been narrowed and is now drawn to one specific gene (ABCA3) but original Claim 5 now broadens Claim 1 by replacing the ABCA3 gene with different genes.

New Necessitated Claim Rejection(s)

Claim Rejections - 35 USC § 112-1st paragraph

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is necessitated by Applicant's amendatory material of judging that said test cancer cell has acquired a drug resistance to etoposides when amplification of the ABCA3 gene is detected in said test cancer cell to claim 1.

Applicant's claimed invention is broad and is generally directed to a method for identifying drug resistant cancer cells. The Applicant's invention involves measuring the

presence or absence of the ATP binding cassette (ABC) transporter gene ABCA3 in a cancer cell to determine if that cell is resistant to the chemotherapy drug etoposide. Claim 1 recites:

> "A detection method of detecting acquisition of a drug resistance of a test cancer cell to etoposides, which comprises detecting the presence or absence of amplification of an ATP binding cassette (ABC) transporter gene, in said test cancer cell by measuring the presence or absence of amplification of the ABC transporter gene in said test cancer cell, wherein said ABC gene is an A3(ABCA3) gene, and judging that said test cancer cell has acquired a drug resistance to etoposides when amplification of the ABCA3 gene is detected in said test cancer cell."

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

The written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not the case involves questions of priority. The requirement applies to all inventions, including chemical inventions, and because the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide a description of the compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

With regard to the description requirement, applicants' attention is invited to consider the decision of the Court of Appeals for the Federal Circuit, which holds that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it form other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genus of etoposide resistance-acquired cancer cells. In addition, no species for the claimed genus of etoposide resistance-acquired cancer cells is provided.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. (see MPEP 2163 II).

In this case, the instant application did not provide core structure or representative number of species for the claimed genus of etoposide resistance-acquired cancer cells.

The instant specification does not disclose common structurally elements shared by the so-called etoposide resistance-acquired cancer cells. Although the instant specification provides certain preferred gene, the ABCA3 gene, the exact criteria for the etoposide resistance-acquired cancer cells are not clearly described. The terms "judging that said test cancer cell has acquired a drug resistance to etoposides when amplification of the ABCA3 gene is detected" are not limiting in defining the amount of amplification required to obtain resistance. Thus, the term "judging that said test cancer cell has acquired a drug resistance to etoposides when amplification of the ABCA3 gene is detected" is very broad and not limiting to specific etoposide resistance-acquired cancer cells.

It is not known in the art that all the etoposide resistance-acquired cancer cells are known, as evidenced by the instant specification that identified only a list of genes (page 17 list and Tables 1-3. Thus, applicants do not appear to have possession of the entire claimed genus of

etoposide resistance-acquired cancer cells. One of ordinary skilled in the art would not be able to identify etoposide resistance-acquired cancer cells. Without identifying the required genes and amount of amplification of each gene that can be used to determine whether the sample contains etoposide resistance-acquired cancer cells, the claimed method for identification of etoposide resistance-acquired cancer cells cannot be conducted.

The claims encompass the use of ANY etoposide resistance-acquired cancer cells. This includes a very diverse and large group of etoposide resistance-acquired cancer cells to which the claims are drawn.

The specification has not provided one single effective example of "judging that said test cancer cell has acquired a drug resistance to etoposides when amplification of the ABCA3 gene is detected in said test cancer cell". In Table 2 the Applicant has screened 13 types of ABC transporters against 19 types of drug-resistant cells. With regards to the claimed ABCA3 gene it has an increase in copy number 7 vs 3 or 5 vs 4 comparing two different cell lines, the parent cell line and the drug-resistant cell line. Other ABC transporter genes also show increases in copy number for these two cell lines. It is not clear how much the ABCA3 gene copy number has to be increased for judging that said test cancer cell has acquired a drug resistance to etoposides when amplification of the ABCA3 gene is detected in said test cancer cell. It is not clear if, as in the instant claim, the ABCA3 gene is the only gene responsible for the test cancer cell to acquire a drug resistance to etoposides. Efferth (03/2001) Current Molecular Medicine volume 1 pages 45 to 65 teaches that amplification of the ABCC1 gene, also listed as having an increased copy number in Table 2 for the same 2 cell lines, results in the test cancer cell to acquiring a drug resistance to etoposides (page 51 left center).

The Applicant's other evidence for the amplification of the ABCA3 gene being only gene responsible for the test cancer cell to acquire a drug resistance to etoposides is presented in Figure 2 a Northern blot of poly (A) RNA comparing the parent cell line HT-29 with the etoposide resistant child cell line HT-29/ETP. Figure 2 shows that while the ABCA3 mRNA has increased expression, so does the ABCC1 mRNA.

Thus, the Applicant has merely screened ABC genes in some drug-resistant cell lines. The Applicant has identified that in two drug-resistant cell lines the ABCA3 gene has an increased copy number. The Applicant has identified in one etoposide-resistant cell line that the ABCA3 gene mRNA expression has increased. However, correlation does not imply causation. The Applicant has not isolated the one claimed variable, the ABCA3 gene in any comparison of parent and child etoposide-resistant cell lines. Since cancer cells are unstable can contain numerous changes in gene expression, some of which have been identified by the Applicant, it is not possible to "judge" that changes in the ABCA3 gene amplification identify cancer cells as drug-resistant.

In addition, the Applicant's data teaches away from the ABCA3 gene as causing drug-resistance in the two tested cell lines because in both cases the ABCC1 gene is amplified also. Since Efferth (03/2001) Current Molecular Medicine volume 1 pages 45 to 65 teaches that amplification of the ABCC1 gene results in the test cancer cell to acquiring a drug resistance to etoposides (page 51 left center), the fact that the two tested cell lines both contain amplified ABCC1 is the most likely explanation for the acquisition of etoposide-resistance in these two cell lines.

Thus, the Applicant has failed to isolate the effects of the known ABCC1 gene from the claimed ABCA3 gene. The present specification does not provide sufficient evidence showing the correlation acquisition of etoposide-resistance in cancer cells with the ABCA3 gene. The present specification does not state what specific amount of ABCA3 gene amplification is required for the acquisition of etoposide-resistance in cancer cells. The working examples do not provide scientific data showing how and if the modulation of the expression of the ABCA3 gene correlates with the acquisition of etoposide-resistance in cancer cells.

The specification provides a generic teaching of etoposide-resistance in cancer cells. However, the specification does not teach the amount of etoposide exposure that determines etoposide-resistance in cancer cells.

The art teaches that many factors need to be considered in order to develop a reliable test for marker analysis and to subsequently determine the drug-resistance in cancer cells. The Valid Concerns Editorial (01/27/2010) Nature volume 463 pages 401 to 402 states "But most new biomarker candidates fall by the wayside and are not pursued — even those first published in high-profile journals. Identifying potential candidates is only the first step. The initial validation must be done to a sufficiently high standard and reported in enough detail for the study to be assessed and reproduced, thereby allowing the best candidates to be identified and taken further. Validation seems to be a major stumbling block." and "One of the main criticisms from our referees of such studies is that the methods are not presented in sufficient detail for the studies to be effectively refereed or repeated. We ask authors to ensure that, where patient studies reveal potential disease biomarkers, the initial validation is conducted to a robust standard and all methods and statistical analyses are reported in sufficient detail to allow the study to be repeated.

Specifically, the manuscript should contain detailed information about the patient and control cohorts, the criteria for inclusion of patient samples and the methods for obtaining and preparing the samples. Any algorithms used to generate a signature should be described in sufficient detail to allow repetition."

There are two basic types of genetic and environmental expression tests - diagnosis and prognosis. The medical dictionary of Marriam-Webster and MedlinePlus defines diagnosis as "the art or act of identifying a disease from its signs and symptoms" and prognosis as "the act or art of foretelling the course of a disease". An example of a test for diagnosis is measuring cardiac troponin I or T in blood serum as a diagnostic tool for acute myocardial infarction [Ladugger (2000) Circulation volume 102 pages 1221 to 1226]. An example of a genetic test for prognosis is measuring BRCA1 and BRCA2 gene mutations to predict the lifetime risk of breast cancer [Mctcalfe (06/15/2004) Journal of Clinical Oncology volume 22 pages 2328 to 2235]. An example of an environmental test for prognosis is measuring cholesterol and low density lipoprotein concentrations in blood serum to predict the risk of cardiovascular disease [Lowe (2000) Thrombosis and Haemostasis volume 84 pages 553 to 558].

The timing of the cardiac troponin I or T test influences the results. "The accuracy of the test decreases with time after the onset of the ischemic event. This increases the risk of false-negative diagnosis in patients with minor myocardial damage and late admittance to the emergency department." [Ladugger (2000) Circulation volume 102 pages 1221 to 1226].

In the cardiac troponin I and T or cholesterol and low density lipoprotein blood tests the result of individual patient samples are compared to a specific numeric reference. In the case of cholesterol and low density lipoprotein the reference is adjusted to match the patient. For

example, an 80 year old male smoker will have different cholesterol and low density lipoprotein references than a 20 year old female nonsmoker [Lowe (2000) Thrombosis and Haemostasis volume 84 pages 553 to 558].

Prognostic tests provide specific statistical risk results. "The risk of contralateral breast cancer in women with a BRCA mutation is approximately 40% at 10 years." [Mctcalfe (06/15/2004) Journal of Clinical Oncology volume 22 pages 2328 to 2235].

Zimmern (05/24/2007) Journal of Public Health volume 1 pages 1 to 5 discusses various limitations and challenges associated with evaluation of genetic tests. Zimmern teaches "The complexities associated with the interpretation of tests for these common disorders and the technologies involved, will be far greater than for genetic tests used in the diagnosis of high penetrance monogenic disorders. Current gaps in methodology, information needs, policies and systems will need to be addressed before such complex evaluations can be undertaken." (page 4, Conclusions).

Shalon (12/13/2001) US Patent Application Publication US 2001/0051344 A1 teaches that variations of genetic make-up within populations lead to various differences in gene expression among genes between any two individuals which may or may not be significant (page 10, paragraph [0155]). Shalon further teaches that the larger the number if individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (page 10, paragraph [0156]). Shalon further teaches that the test pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically

at least 2 fold and up to 100 fold or more, an increase or decrease in gene expression level with respect to control levels for the same gene (page 10, paragraph [0158]).

Kroese (12/2004) Genetics in Medicine volume 6 pages 475 to 480 teaches genetic tests that are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese teaches that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods (page 476 column 2). Kroese further teaches that a genetic test is shorthand for a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristic of a genetic test is evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence interval (page 477 column 1).

Lucentini (12/20/2004) The Scientist volume 18 pages 20 to 23 teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (page 21). He further teaches that bigger sample sizes and more family based studies, along with revising statistical methods, should be included in gene association studies (page 22).

Tainsky (07/10/2007) Biomarker Insights pages 261 to 267 discusses the early detection of cancer using genomic and proteomic technologies. Tainsky teaches "The prospects of diagnostic tests for the early detection of cancer using genomic and proteomic technologies have opened a Pandora's Box of questions on the steps in development of clinical tests. Formatting the reagents into a configuration that is amenable to a clinical laboratory is a rather daunting barrier to a successful clinical test. Even the development of a generic approach to measure 20–100

analytes will require solutions to some unique optimization challenges. Formatting the complete diagnostic test will be more than 20 to 100 times the cost of formatting a single test. A major barrier in multianalyte diagnostics will be the large number of controls and standards required for such a test. To insure tests work properly during development, during production and in customer laboratories, kits require controls and calibrators. This is particularly important for protein-based diagnostics. Controls for this approach may consist of cancer patient sera or potentially panels of human recombinant proteins for each biomarker. Because patient sera containing these biomarkers will be in short supply, the alternative approach of using recombinant proteins for each biomarker is much preferable. However, preparing such recombinant proteins as controls although feasible is clearly a substantial technical challenge." (page 261 bottom).

Miklos (05/2004) Nature Biotechnology volume 22 pages 615 to 621 discusses using expression data with complex diseases. Miklos teaches "A problem in analyzing microarray-based gene expression data is the separation of genes causally involved in a disease from innocent bystander genes, whose expression levels have been secondarily altered by primary changes elsewhere. To investigate this issue systematically in the context of a class of complex human diseases, we have compared microarray-based gene expression data with non-microarray-based clinical and biological data about the schizophrenias to ask whether these two approaches prioritize the same genes. We find that genes whose expression changes are deemed to be of importance from microarrays are rarely those classified as of importance from clinical, in situ, molecular, single-nucleotide polymorphism (SNP) association, knockout and drug perturbation data. This disparity is not limited to the schizophrenias but characterizes other human disease

data sets. It also extends to biological validation of microarray data in model organisms, in which genome-wide phenotypic data have been systematically compared with microarray data. In addition, different bioinformatic protocols applied to the same microarray data yield quite different gene sets and thus make clinical decisions less straightforward. We discuss how progress may be improved in the clinical area by the assignment of high-quality phenotypic values to each member of a microarray-assigned gene set." (page 615 left top).

As discussed above, the Applicant has failed to identify even one single species of the claimed genus of etoposide-resistant cancer cells caused by the amplification of the ABCA3 gene. Thus, applicant's claimed scope represents only an invitation to experiment regarding possible involvement of the amplification ABCA3 gene for use in "judging" the acquisition of etoposide-resistance in cancer cells.

Claim Rejection(s) Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
5. Secondary considerations (objective evidence of nonobviousness): a) commercial success; b) long felt need; c) evidence of unexpected results; d) skepticism of experts; and e) copying.

Claims 1 and 3-8 are obvious over Watts in view of Efferth and Wessendorf:

Claims 1 and 3-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts (11/2001) The Journal of Pharmacology and Experimental Therapeutics volume 299 pages 434 to 441 in view of Efferth (03/2001) Current Molecular Medicine volume 1 pages 45 to 65 and Wessendorf (01/2002) Laboratory Investigation volume 82 pages 47 to 60. This rejection has been modified due to the Applicant's amendment adding the limitation of claim 2 into claim 1 and adding judging that said test cancer cell has acquired a drug resistance to etoposides when amplification of the ABCA3 gene is detected in said test cancer cell to claim 1.

Applicant's claimed invention is broad and is generally directed to a method for identifying drug resistant cancer cells. The Applicant's invention involves measuring the presence or absence of the ATP binding cassette (ABC) transporter gene ABCA3 in a cancer cell to determine if that cell is resistant to the chemotherapy drug etoposide. Claim 1 recites:

> "A detection method of detecting acquisition of a drug resistance of a test cancer cell to etoposides, which comprises detecting the presence or absence of amplification of an ATP binding cassette (ABC) transporter gene, in said test cancer cell by measuring the presence or absence of amplification of the ABC transporter gene in said test cancer cell, wherein said ABC gene is an A3(ABCA3) gene, and judging that said test cancer cell has acquired a drug resistance to etoposides when amplification of the ABCA3 gene is detected in said test cancer cell."

Regarding **claims 1 and 5**, Watts teaches a detection method of detecting acquisition of a **drug resistance** of a test cancer cell to etoposides, which comprises **detecting the presence or absence of amplification** of an **ATP binding cassette (ABC) transporter gene**, in said test cancer cell by measuring the presence or absence of amplification of the ABC transporter gene **in said test cancer cell**, and **judging that said test cancer cell has acquired a drug resistance** when amplification of the ABC gene is detected in the test cancer cell, e.g., Figure 1, Figure 2, Figure 3a, and

> "In the human multiple **myeloma cell** line, RPMI 8226, doxorubicin selection at 60 nM resulted in a resistant variant, 8226/Dox6. Further selection of 8226/Dox6 with 400 nM doxorubicin led to the highly resistant 8226/Dox40 cell line. Both 8226/Dox cell lines possess a **multidrug-resistant** phenotype." (page 434 left bottom) and "we have analyzed the RPMI 8226 cell line and its **multidrug-resistant** variants, 8226/ Dox6 and 8226/Dox40, using 5760-element cDNA microarrays to identify differential gene expression." (page 435 left bottom) and " the **MDR1 gene** was identified as differentially expressed between RPMI 8226 and the 8226/Dox cell lines in a all replicates (Fig. 1)." (page 436 right center) and "Figure 3a shows a progressive increase in **MDR1 mRNA expression** from none in RPMI 8226 to an intermediate level in 8226/Dox6 and finally **a high level of expression** in 8226/Dox40."

page 436 right bottom. MDR1 is another name for the ABCB1 gene.

Regarding **claims 3-4**, Watts teaches detection is carried out by the **DNA chip** method, e.g., Figure 1 and

> "we have analyzed the RPMI 8226 cell line and its multidrug-resistant variants, 8226/ Dox6 and 8226/Dox40, using 5760-element **cDNA microarrays** to identify differential gene expression." (page 435 left bottom) and "the MDR1 gene was identified as differentially expressed between RPMI 8226 and the 8226/Dox cell lines in a all replicates (Fig. 1)."

page 436 right center.

Regarding **claim 6**, Watts teaches a substrate used in the **DNA chip** method is a DNA fixed substrate wherein the DNA comprises one or more types of genes selected from ABC transporter genes consisting of **ABCB1**, for example, Figure 1, Figure 2, Figure 3a, and

> "we have analyzed the RPMI 8226 cell line and its multidrug-resistant variants, 8226/ Dox6 and 8226/Dox40, using 5760-element **cDNA microarrays** to identify differential gene expression." (page 435 left bottom) and " the **MDR1 gene** was identified as differentially expressed between RPMI 8226 and the 8226/Dox cell lines in a all replicates (Fig. 1)." (page 436 right center) and "Figure 3a shows a progressive increase in **MDR1 mRNA expression** from none in RPMI 8226 to an intermediate level in 8226/Dox6 and finally a high level of expression in 8226/Dox40."

page 436 right bottom. MDR1 is another name for the ABCB1 gene.

Regarding **claim 7**, Watts teaches allowing **control DNAs** and the DNA of a test cancer cell used as a target of detection of acquisition of **drug resistance**, each of which was **labeled with each different fluorescent dye**, to simultaneously contact with said **DNA-fixed substrate**, so as to conduct hybridization; and quantitatively **detecting amplification or deletion** of a specific region of the test DNA by using the fluorescent dye obtained as a result of the **hybridization as an index**, for example, Figure 1, and

> "In the human multiple myeloma cell line, **RPMI 8226**, doxorubicin selection at 60 nM resulted in a resistant variant, 8226/Dox6. Further selection of 8226/Dox6 with 400 nM doxorubicin led to the highly resistant 8226/Dox40 cell line. Both 8226/Dox cell lines possess a **multidrug-resistant** phenotype." (page 434 left bottom) and "we have analyzed the RPMI 8226 cell line and its **multidrug-resistant** variants, 8226/ Dox6 and 8226/Dox40, using 5760-element **cDNA microarrays** to identify **differential gene expression**." (page 435 left bottom) and " the **MDR1 gene** was identified as differentially expressed between RPMI 8226 and the 8226/Dox cell lines in a all replicates (Fig. 1)." (page 436 right center) and "**Labeled cDNA** from two reactions (one **Cy3-labeled, one Cy5-labeled**) was combined and purified on a microcon-50 column using four buffer exchanges ...." (page 436 left top) and "Slides were scanned for **Cy3 and Cy5 fluorescence** using a Axon GenePix 4000 microarray reader (Axon Instruments, Foster City, CA) and **quantitated** using GenePix software. The RPMI 8226

> versus 8226/Dox6 hybridizations were performed in triplicate, and the **RPMI 8226 versus 8226/Dox40 hybridizations** were performed seven times."

page 436 left top.

While Watts teaches a method of detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs by detecting amplification of ABC transporter genes in a test cancer cell, Watts does not teach the ABCA3 gene as recited in claims 1 and 5 or etoposides as recited in claim 1 or genomic DNA as recited in claim 8.

Regarding **claim 1**, Efferth teaches a detection method of detecting acquisition of a **drug resistance of a test cancer cell to etoposides**, which comprises **detecting the presence or absence of amplification** of an **ATP binding cassette (ABC) transporter gene**, in said test cancer cell by measuring the presence or absence of amplification of the ABC transporter gene **in said test cancer cell**, and **judging that said test cancer cell has acquired a drug resistance** when amplification of the ABC gene is detected in the test cancer cell, e.g.,

> "**ABCC1** (MRP1) has been first identified in a multidrug-resistant, P-glycoprotein negative lung cancer cell line .... MRP1 acts as a drug-efflux pump **rendering cancer cells resistant to cytostatic drugs**.... Evidence for a causative contribution of MRP1 to drug resistance came from **transfection experiments** ...." (page 51 left center) and "MRP2 is involved in the **development of multidrug resistance** as well as in resistance to cisplatin or methotraxate resistance, both of which are not involved in the classical multidrug resistance phenotype" (page 51 right bottom) and "The ABCC3 (MRP3) gene is probably not responsible for the Dubin-Johnson syndrome, since MRP3 is expressed in the liver of Eisai hyperbilirubinemic rats and TR(-) mutant rats. It is involved in **anticancer drug resistance** ...." (page 52 left top) and "identified the ABCC6 (MRP6) gene in **epirubicin-resistant leukemia cells**." (page 52 left center) and "Unraveling ABC transporter genes as responsible factors for resistance to cancer chemotherapy has opened new avenues for diagnosis of **drug-resistant tumors**."

page 56 left bottom.

Regarding **claims 1 and 5**, Efferth teaches types of genes selected from ABC transporter genes including the **ABCA3 gene** e.g., Table I and Table II.

Regarding **claim 1**, Efferth teaches a detection method of detecting acquisition of a drug resistance of a test cancer cell to **etoposides**, e.g.,

> "This indicates that MRP1 exports drugs out of the cell and sequestrates drugs into vesicles. MRP1 knock-out mice are hypersensitive to **etoposide**, especially in bone marrow, testis, and kidney.... MRP1 has various functions: 1. transport of exogenous allocrites: a. anticancer drugs, i.e. doxorubicin, **etoposide**, or vincristine...."

page 51 left bottom.

While Watts and Efferth teach a method of detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs by detecting amplification of ABCA3 transporter gene in a test cancer cell, Watts and Efferth do not teach genomic DNA as recited in claim 8.

Regarding **claim 8**, Wessendorf teaches DNA fixed on said DNA-fixed substrate, test DNA, and control DNA are **genomic DNAs**, for example, Figure 2 and

> "we investigated the potential of matrix-CGH using universally amplified **genomic DNA** from three tumor cell samples (see Fig. 2)...."

page 49 left center.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to provide Watts's method of detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs by detecting amplification of ABC transporter genes in a test cancer cell in Efferth's method of detecting acquisition of the drug resistance of a test cancer cell to etoposides by detecting amplification of ABCA3 in a test cancer cell and in Wessendorf's

method screening using genomic DNA to arrive at applicant's invention with the above cited references before them.

The present claims would have been obvious because the substitution of one known element the MDR1 gene, taught by Watts for another the ABCA3 gene, taught by Efferth would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs by detecting amplification of ABCA3 gene in a test cancer cell).

The present claims would have been obvious because the substitution of one known element doxorubicin, taught by Watts for another etoposides, taught by Efferth would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. detecting acquisition of the drug resistance of a test cancer cell to etoposides by detecting amplification of ABC transporter genes in a test cancer cell). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

The present claims would have been obvious because the substitution of one known element cDNA, taught by Watts for another genomic DNA, taught by Wessendorf would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs by detecting amplification of genomic ABC transporter genes in a test cancer cell).

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Common Ownership of Claimed Invention Presumed

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Discussion and Answer to Argument

Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of Applicant's traversal is addressed below (Applicant's arguments are in italic):

1. Applicant asserts "Tables 1 and 2 of Efferth, describe the ABCA3 gene simply as one type of ABC transporter. That is, Efferth does not teach or suggest that the ABCA3 gene is involved in drug resistance, especially in etoposide drug resistance. Instead, Efferth describes that the ABCCl(MRP 1) gene is involved in drug resistance of tumors, and that the ABCBl gene is involved in the drug resistance of cancer, see page 51 and pages 48-50 of Efferth, respectively.

Efferth further discloses that some ABC transporter genes are involved in drug resistance. However, as noted above, Efferth does" (Reply page 6 bottom) and "Applicants submit that an ordinary artisan would not have been motivated to combine Watts with Efferth. Further, even if Watts were combined with Efferth, this combination does not describe that the ABCA3 gene is involved in etoposide resistance." (Reply page 7 top).

In response to Applicant's arguments, the Examiner respectfully disagrees. Applicant's traversed the above rejection over the combination of the cited references by traversing specific sections of the Efferth reference alone. In response to Applicant's arguments against the parts references individually, one cannot show nonobviousness by attacking parts references individually where the rejections are based on combinations of parts and references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants are respectfully directed to the body of the rejection above for detailed discussion of how the combination of the cited references teaches all elements and renders the instant claimed invention obvious.

Specifically, Efferth teaches many ABC transporter genes are involved in drug-resistant tumors and there are 47 members of known ABC transporters including ABCA3 of the instant claims. Efferth teaches these 47 members share similar architecture and all function as "traffic ATPases". Efferth teaches ABCB1 (MDR1) causes doxorubicin-resistant tumors and ABCC1 (MRP1) causes etoposide-resistant tumors. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowed.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to CHRISTIAN BOESEN whose telephone number is 571-270-1321. The Examiner can normally be reached on Monday-Friday 9:00 AM to 5:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher S. Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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